REMARKS

The Claims

Claims 45-60 are currently pending in the application. Claims 45, 48 and 49 have been amended and Claims 61-78 have been added. The new and amended claims are fully supported by the specification. For example, recitation of one, two, three, four, and more than four additional glcyosylation sites is found at p. 13, lines 14-25 of the specification. No new matter has been introduced and no issues requiring further consideration and/or search have been raised by the new claims. Entry of the claims is respectfully requested.

Claim objections

Claim 47 and 48 are objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of the previous claim. The Examiner argues that Claims 47 and 48 have subsitutions at sites which are not recited in the independent claim. Applicants disagree.

Claims 47 and 48 depend from Claim 46. Claim 46 recites an analog of human erythropoietin which has one or more additional glycosylation site(s), where one such site is introduced at position 52, 53, 55, 86 or 114. In other words, the analog may have one or more (i.e., one, two, three, four or more) additional glycosylation sites) provided that one of the sites is introduced at any one of the specified positions 52, 53, 55, 86 or 114. This interpretation of Claim 46 is supported by the specification at p. 13, lines 9-14 ("The new analogs will have at least one new N-linked glycosylation site at any of positions 52, 53, 55, 86 and 114 and may further comprise additional N-linked or O-linked carbohydrate chains at other site").

Thus, Claim 47 meets the limitations of Claim 46 by reciting an analog having additional glycosylation sites, including one at position 114. Claim 48 meets the limitations of

Claim 46 by reciting that the analog further comprises an additional glycosylation site at position 125 (in addition to one glycosylation site at position 52, 53, 55, 86 or 114). Applicants maintain that Claims 47 and 48 properly limit the parent claim.

Rejections under 35 U.S.C. 112

Claims 45 and 51-60 are rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly does not enable one skilled in the art to make and/or use the invention. The Examiner argues that the recitation of N-linked glycosylation sites "at about" a position in the amino acid sequence of human erythropoietin is not taught by the specification. It is argued that the specification is not enabled for "any amino acid change which would provide an N-linked glycosylation site" because the specification allegedly teaches Epo hyperglycosylated analogs with lower *in vitro* activity compared to rHuEpo, suggesting that changing certain amino acid residues in human erythropoietin can affect biological activity.

The Examiner has not established a *prima facie* case of nonenablement. In the first instance, the Examiner appears to suggest that the rejected claims are directed to amino acid changes at any position in human erythropoietin provided such changes provide an N-linked glycosylation site. Claim 45, as amnended is directed to a new N-linked glycosylation site at about position 114, rather than at any position. Clearly, Claim 45 would not require one to generate an "infinite number of derivatives" as is alleged by the Examiner. Thus, the scope of the claim (and the scope of enablement which is required) is different from that alleged by the Examiner.

Applicants clearly enable the scope of Claim 45 as the specification contemplates and teaches the introduction of new N-linked glycosylation sites in human erythropoietin at about position 114. In view of these extensive teachings, the working examples in the present application and the state of the prior

art relating to introduction of new glycosylation sites in human erythropoietin, undue experimentation would not be required.

Secondly, the Examiner's arguments relating to alleged lower *in vitro* activity of certain hyperglycosylated Epo analogs disclosed in the application do not support the case for nonenablement. The Examiner appears to be referring to Table 2 on p. 36 which lists the *in vitro* activity of 13 analogs (designated N49 through N61) as compared to recombinant human Epo (rHuEpo). Nine of the analogs had *in vitro* activity equivalent to that of rHuEpo whereas two analogs (N53 and N59) had *in vitro* activity which was reported to be 25-75% that of rHuEpo. The remaining two analogs were not tested for *in vitro* activity. The data represented in Table 2 indicate that none of the amino acid changes that were made to create new N-linked glycosylation sites abolished *in vitro* activity and only two of 13 analogs showed any reduction in *in vitro* activity. The specification is clearly sets forth guidance for making a number of new N-linked glycosylation analogs which retain some or all of the *in vitro* activity of rHuEpo. Contrary to the Examiner's position that the specification is an "invitation for further experimenation", there is substantial guidance as to glycosylation analogs of human erythropoietin that may be constructed.

Further, Applicants also note that one analog (N53) which was observed to have somewhat reduced *in vitro* activity actually had significantly greater *in vivo* activity than rHuEpo (see Figure 3 and Example 3). This suggests that even though *in vitro* activity of a glycosylation analog may be reduced, *in vivo* activity in the same analog can be enhanced. This provides further evidence that the specification would allow one skilled in the art to make the claimed analog without undue experimentation.

It is requested that the rejection be withdrawn.

Claims 45 and 51-60 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. The Examiner argues that the term "at about position" is a relative term that

renders the claim indefinite and further alleges that the scope of the invention would be indefinite.

Applicants maintain that the term "about" is clear and definite to one skilled in the art based upon the disclosure. For example, the specification teaches the addition of an N-linked glycosylation site (and carbohydrate chain) to human erythropoietin at position 52, 53, or 55 (see Table I in the examples). In this example, one skilled in the art would understand that an N-linked carbohydrate chain at position 53 is at "about" position 52 or at "about" position 55. The meaning and scope of the invention may be ascertained by one skilled in the art and the term "about" is not indefinite.

Rejection under 35 U.S.C. 102

Claims 45 and 51-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Elliott et al. (PCT publication no. WO95/05465; reference BC submitted by Applicants). It is argued that one or more of the presently claimed analogs are disclosed in Elliott et al., with the disclosure of those analogs with new N-glycosylation sites at positions 30, 51, 57, 69, 88, 89, 136 or 138.

Solely to advance prosecution, Applicants have amended Claim 45 to recite that one additonal glycosylation site is introduced at about position 114. It is requested that the rejection be withdrawn.

Rejection under 35 U.S.C. 103

Claims 53, 54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott et al. (cited above) in view of U.S. Patent No. 5,559,093 to Yoshitomi et al. (hereafter, the "'595 patent").

Claim 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott et al. (cited above) in view of U.S. Patent No. 5,416,071 to Igari et al. (hereafter, the "'071 patent").

Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott et al. (cited above) in view of U.S. Patent No. 6,548,653B1 to Young et al. (hereafter, the "'653 patent").

Claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliott et al. (cited above) in view of U.S. Patent No. 4,806,524 to Kawaguchi et al. (hereafter, the "'524 patent")

It is argued that it would have been obvious to modify the teachings of Elliott et al. to make a presently claimed analog (namely, an analog of human erythropoietin comprising the amino acid sequence of human erythropoietin from residues 1-165 as shown in SEQ ID NO:1 except for one or more amino acid changes which provide for one or more additional glycosylation site(s) as compared to human erythropoietin, wherein one additional site is introduced at about position 52, 53, 55, 86 or 114 and an N-linked carbohydrate chain is attached at said one additional site) and any one of the formulation components as disclosed in either the '595 patent (sodium citrate, human serum albumin and benzyl alcohol), the '071 patent (tween), or the '653 patent (ascorbic acid). In using similar arguments, the Examiner argues it would have been obvious to modify the teachings of Elliott to make a presently claimed analog for use in liquid or lyophilized forms, as liquid or lyophilized form of erythropoietin were allegedly being taught in the '524 patent.

Solely to advance prosecution, Applicants have amended Claim 45 to recite that one additonal glycosylation site is introduced at about position 114 and request that the rejection be withdrawn.

CONCLUSION

Claims 45-78 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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